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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/12, 9/16, 31/57

A1

(11) International Publication Number: WO 99/53901

(43) International Publication Date: 28 October 1999 (28.10.99)

(21) International Application Number: PCT/EP99/02535

(22) International Filing Date: 15 April 1999 (15.04.99)

(30) Priority Data:

9808152.4	18 April 1998 (18.04.98)	GB
9814709.3	8 July 1998 (08.07.98)	GB

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(54) Title: PHARMACEUTICAL AEROSOL FORMULATION

(57) Abstract

The present invention relates to novel pharmaceutical aerosol formulations comprising: (A) a therapeutic agent in the form of particles coated by at least one coating excipient and at least one surfactant, in suspension in (B) a liquefied propellant gas for the administration of therapeutic agents particularly by the pulmonary route and to a process for preparing these formulations. It also relates to novel particles suitable for use in such formulations.

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Pharmaceutical aerosol formulation

The present invention relates to novel pharmaceutical aerosol formulations for the administration of therapeutic agents particularly by the pulmonary route and to a process for preparing these formulations. It also relates to novel particles suitable for use in such formulations.

The use of aerosols for the administration of medicaments by the peripheral aerial pathways has been known for several decades. Such aerosols generally contain the therapeutic agent, one or more adjuvants such as solvents or surfactants and one or more propellants.

The most commonly used propellants in the past are chlorofluorocarbons, such as CCl_3F (Freon® 11), CCl_2F_2 (Freon® 12) or CF_2ClCF_2Cl (Freon® 114). However, the recent phasing out of these propellant gases due to their harmful effect on the ozone layer has caused manufacturers of aerosol sprays to use new propellant gases which protect stratospheric ozone.

Such "ozone-friendly" gases, also known as green gases, for example encompass hydrogen-containing chlorofluorocarbons, hydrogen-containing fluorocarbons and perfluorocarbons.

A specific group of therapeutic agents administered by the pulmonary route are antiasthmatics including bronchodilators and antiinflammatories of steroid type having a local therapeutic action in the lungs and/or a systemic therapeutic action after absorption in the blood.

For such medicaments, the replacement of the usual chlorofluorocarbon propellants by the novel propellants which protect the ozone layer can be accompanied by problems of stability of the suspensions.

This is because the change in the polarity of the propellant sometimes results in a partial solubility of the drug in the gas. This partial solubility may lead to an undesirable increase in the size of the particles during storage and/or the formation of aggregates. The valves of the administration device are then observed to block and/or the aggregates of particles penetrate less well into the fine lower respiratory pathways.

International Patent Application No. WO 92/08446 (Glaxo Group Limited) and EP-A-0 493437 (Riker Laboratories Inc) disclose the presence of surfactants in pharmaceutical aerosol formulations, however, the use of lactose or other sugars is not described. WO 94/03153 (Glaxo Group Limited) discloses a suspension formulation of beclomethasone dipropionate, but specifically excludes the presence of a surfactant. WO 93/11743, WO 93/11744 and WO 93/11745 (Glaxo Group Limited) also disclose suspension formulations of drugs which specifically exclude the presence of surfactant. WO 97/35562 (Danbiosyst) describes the process of incorporating a drug into polysaccharide microspheres by spray drying, however, the use of disaccharides, such as lactose in such a process is specifically excluded. Furthermore, there is no disclosure of their use in formulations containing a liquefied propellant gas. WO 91/16882 (Liposome Technology) discloses a process for spray drying a drug/lipid-containing ethanol solution, but there is no mention of employing a surfactant in this process. EP-A-550031 (Hoechst) discloses pressurised aerosol formulations containing spray-dried product, wherein the spray-dried product is obtained by spray-drying a solution of drug, surfactant and (optionally) auxiliary substance to give a finely dispersed matrix.

We have now discovered that it is possible to improve the stability of suspensions of drugs in the propellant by protecting the drug particles from the propellant gas with a coating. This protective layer prevents the partial solubilization of the drug in the propellant and the formation of aggregates. In combination with a surfactant, this coating excipient thus makes it possible to obtain aerosol formulations for pulmonary administration which, protected from atmospheric moisture, are stable for months and make it possible to deliver drug particles having sizes which are sufficiently small to penetrate into the respiratory pathways.

A first subject of the present invention is consequently a pharmaceutical aerosol formulation comprising a therapeutic agent in the form of coated particles in suspension in a propellant.

A further subject of the present invention is the process for preparing these particles and pharmaceutical formulations.

A still further subject are the coated drug particles.

Further subjects will become apparent to those skilled in the art from the following description and examples.

The present invention thus provides pharmaceutical aerosol formulations comprising

(A) a therapeutic agent in the form of particles coated by at least one coating excipient and at least one surfactant, in suspension in

(B) a liquefied propellant gas

The therapeutic agents which can be used in these aerosol formulations are all solid drugs which can be administered by the pulmonary route and which are insoluble, or very slightly soluble, in the medium which is used to coat the drug particles.

A drug is regarded as insoluble or very slightly soluble if it dissolves to less than 0,1 % (m/v) in the suspending medium used for the coating.

These therapeutic agents encompass in particular bronchodilators and steroidal antiinflammatories commonly used in the treatment of asthma, such as beclomethasone dipropionate, salbutamol (eg as sulphate or free base), salmeterol (eg as 1-hydroxy-2-naphthoate salt), fluticasone propionate or solvates thereof. Other compounds of interest include (2R,3R,4S,5R)-2-[6-Amino-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3,4-diol (eg as maleate salt) and 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid *S*-(2-oxo-tetrahydro-furan-3-yl) ester and 6α,9α-Difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-(2-oxo-tetrahydro-furan-3-yl) ester.

Among these, use is preferably made of beclomethasone dipropionate and in particular of its monohydrate. Use in relation to salmeterol xinafoate is also preferred.

The pharmaceutical formulations may of course also contain a combination of two or more therapeutic agents which can be administered by the pulmonary route. An example of such a combination is fluticasone propionate and salmeterol xinafoate.

The particles are coated, according to the present invention, with a protective layer comprising at least one coating excipient. This coating excipient must be physiologically acceptable when it is used in administration by the aerial pathways. In order to efficiently protect the drug particles, it must in addition be essentially insoluble in the propellant. Furthermore, the process for the preparation of the coating requires that the coating excipient be soluble in the suspending medium used to prepare the formulation, which is preferably an aqueous medium.

A beneficial coating effect can be obtained with a coating layer covering the major surface of the particles. In order to achieve optimal protection of the drug particles at least about 80 % and more preferably at least about 90 % of their surface should be covered by the coating layer.

The coating excipients which satisfy all these requirements are chosen from mono-, di- or polysaccharides, such as mannitol, lactose, trehalose, dextrose, microcrystalline cellulose, sodium carboxymethylcellulose, methylhydroxypropylcellulose or sorbitol.

Among these, use is preferably made of one of the two diglucosides lactose and trehalose.

The drug particles are coated not only with a coating excipient described above but also with at least one surfactant. This surfactant must be physiologically acceptable when it is used by inhalation. It must be insoluble (or essentially insoluble) in the liquefied propellant gas or gases and must not have affinity therewith. This surfactant essentially acts as a stabiliser for the slurry of drug particles in the aqueous coating medium

Examples of surfactants which can be used according to the present invention are anionic surfactants such as oleic acid, non-ionic surfactants such as sorbitan trioleate, sorbitan monooleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monooleate, natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of ethylene oxide and of propylene oxide, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol 400 or glyceryl monolaurate, or cationic surfactants, such as cetylpyridinium chloride or benzalkonium chloride. Other examples of surfactants include synthetic phosphatides eg. distearoylphosphatidylcholine.

Use will preferably be made of lecithin.

The coating of the drug particles of the present invention can optionally comprise, in addition to the surfactant and the coating excipient, a vegetable oil chosen from olive oil, corn oil, cottonseed oil and sunflower seed oil.

The propellant which can be used according to the present invention is any liquifiable fluorocarbon, hydrogen-containing fluorocarbon or hydrogen-containing chlorofluorocarbon having a sufficient vapour pressure to enable it to act as a propellant. The propellant must be essentially non solvent for the coated drug particles, that is to say for the therapeutic agent, the coating excipient and the surfactant. Appropriate propellants include, for example, C_{1-4} hydrochlorofluorocarbons, such as CH_2ClF, $CClF_2CHClF$, CF_3CHClF, CHF_2CClF_2, $CHClFCHF_2$, CF_3CH_2Cl and $CClF_2CH_3$, C_{1-4} hydrofluorocarbons, such as CHF_2CHF_2, CF_3CH_2F, CHF_2-CH_3 and CF_3CHFCF_3, and perfluorocarbons such as CF_3CF_3 and $CF_3CF_2CF_3$, or mixtures of these. Particularly preferred

propellants include CF_3CH_2F, CF_3CHFCF_3 and mixtures thereof. Use is preferably made of a single propellant of hydrofluorocarbon or hydrochlorofluorocarbon type and in particular of 1,1,1,2-tetrafluoroethane (CF_3CH_2F) (HFA 134a).

The coated drug particles of the aerosol formulations of the present invention must have sizes which allow them to be administered by inhalation. The particles must be sufficiently small, on the one hand, to penetrate into the pulmonary pathways without encountering obstacles and, on the other hand, they must have a sufficiently large size to deposit in the lung and not to be carried away by exhalation.

The penetration of the drug particles as far as the pulmonary bronchioli and alveoli is only possible for particles having a mean size of less than 10 µm, preferably of less than 5 µm.

The size of the coated drug particles of the present invention is preferably within the range from 0.5 µm to 10 µm, in particular from 1 µm to 5 µm.

The pharmaceutic compositions according to the invention may also comprise other pharmaceutically acceptable ingredients such as solvents or surfactants. In a preferred embodiment of the present invention, the formulations contain no surfactant besides that coated on the drug particles and no co-solvents.

The present invention also provides a method for preparing a pharmaceutical aerosol formulation which consists in coating drug particles with at least one coating excipient and with at least one surfactant and in packaging them, together with the propellant, in a pressurised cartridge.

The process for the preparation of the pharmaceutical aerosol formulation of the present invention comprises, more specifically, the stages which consist

(a) in preparing a suspension containing

- the therapeutic agent in the form of particles,
- a suspending medium which is a non-solvent for the therapeutic agent,
- the coating excipient dissolved in the suspending medium and
- the surfactant;

(b) in spray drying the suspension of the therapeutic agent obtained in stage (a), so as to obtain drug particles coated by the excipient and by the surfactant;

(c) suspending the coated drug particles obtained in stage (b) in the liquefied propellant gas.

The particles of therapeutic agent used in step (a) will also be of size suitable for inhalation eg of mean size less than 10 μm (eg 0.5 μm - 10 μm) preferably less than 5 μm (eg 1μm - 5 μm).

In one embodiment of the process of the invention, the suspension of stage (a) above is prepared by dissolving the excipient and by dispersing the surfactant in the said suspending medium and by subsequently dispersing the drug particles in the colloidal solution thus obtained.

It is also possible, according to another embodiment of the process of the invention, to adsorb, in a first step, the surfactant on the uncoated drug particles

and subsequently to disperse the particle/surfactant combination in the suspending medium containing, in the dissolved form, the coating excipient.

The suspending medium used for coating of the drug particles has to be essentially non solvent for the therapeutic agent and a good solvent for the coating excipient. The preferred suspending medium is water. The content of therapeutic agent in the suspension prepared in stage (a) can vary within wide limits. It is generally within the range from 1 to 40 % (mass/volume), preferably in the range from 5 to 20 % (mass/volume).

The ratio of the coating excipient to the therapeutic agent in the suspension before spray drying is between 1 and 20 % by weight, preferably between 5 and 10 % by weight.

The ratio of the surfactant to the therapeutic agent in the suspension obtained in stage (a) is generally between 1 and 20 % by weight, preferably between 5 and 10 % by weight.

The suspension described above is subsequently subjected to spray drying in an appropriate device. The suspension to be dried is dispersed as fine droplets in a stream of hot air, which instantaneously transforms them into small grains of powder. A person skilled in the art would know how to adjust the operating parameters, such as the flow rate of the suspension arriving in the drying chamber, the size of the nozzle, the inlet and outlet temperature, the atomising pressure and the flow rate of the atomising air, according to the recommendations of the manufacturer and as a function of the characteristics of the product which he desires to obtain.

A suitable spray dryer which makes possible the drying of the drug particles of the present invention is the Büchi 191 Mini Spray Dryer (Büchi Company, Switzerland). The physical parameters of the atomisation in such a device which make it possible to obtain the coated particles of active principle from the suspension of stage (a) are as follows:

- Inlet air temperature: 110-170°C
- Outlet air temperature: 70-120°C
- Atomising air flow rate: 400-1000 litres per hour (preferably 400-800 litres per hour)
- Pumps speed : 10-45 rpm (preferably 10-15 rpm). Typically this equates to 2-10 litres per minute (preferably around 3ml per minute).

The spray-dried material obtained is composed of particles having a mean size of between 1 mm and 10 μm and a water content of between 0.1 and 5 % by weight.

Another suitable spray dryer which makes possible the drying of the drug particles of the present invention is the NIRO Minor Mobile Spray Dryer. The physical parameters of the atomisation in such a device which make it possible to obtain the coated particles of active principle from the suspension of stage (a) are as follows:

- Inlet air temperature: 100 – 220°C
- Outlet air temperature: 60 – 120°C
- Atomising air flow rate: 50 – 130 m^3/h
- Suspension flow rate : 300 – 5000 ml/h

The spray-dried material obtained is composed of particles having a mean size of between 0.1 μm and 10 μm and a water content of between 0.1 and 5 % by weight.

If necessary, the particles obtained by spray drying can be subjected to micronisation or to any other method which is able to reduce their mean size to a value of less than 10 μm and preferably of less than 5 μm. Indeed, spray drying may result in partial aggregation of the particles bound to each other by the coating layer, this aggregation increasing substantially the apparent mean size of the particles.

The main purpose of this step is to break up these aggregates. It is optional and its usefulness depends, of course, on the presence of aggregates, in other words on the size of the particles after spray drying.

Micronisation is carried out in devices known as compressed-air micronisers or fluid jet mills. In these devices, the particles are carried by a strong stream of air into a chamber designed so that the particles are subjected therein to a large number of impacts. According to the invention, in order to obtain coated drug particles having an appropriate size, these devices will be made to operate at a pressure of between 8 and 14 bar, preferably between 9 and 12 bar.

The cartridges may be filled by any means which makes it possible to obtain a homogeneous suspension of the coated drug particles in the propellant. The cartridges can be filled, for example, first with the powder and then with the propellant ('dual stage') or alternatively with a prepared suspension of the powder in the propellant ('single stage').

This filling will preferably be carried out in a controlled atmosphere with a low relative humidity, in order to limit the hydration of the particles during filling.

Cartridges will generally be fitted with a metering valve and a metered dose inhaler (MDI) will comprise such a cartridge and valve together with a channelling device suitable for delivery of the formulation to the lung.

The cartridges are preferably but not necessarily stored in a packaging composed of a film which is impermeable to atmospheric moisture. The suspensions contained in these overwrapped cartridges are stable for several months at room temperature (25°C). Other means to resist ingress of moisture to the canister may also be employed.

Examples

The following examples are intended to illustrate the invention but do not have a limiting nature.

Example 1

0.5g of lactose and 0.5g of lecithin are dissolved in 100ml of demineralized water at room temperature. After obtaining a colloidal solution, 5g of beclomethasone dipropionate monohydrate (BDP) as micronised particles are dispersed with stirring in the aqueous solution. The suspension thus obtained contains 5% BDP, 0.5% lecithin and 0.5% lactose.

This suspension is then spray-dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:

- Inlet air temperature : 160°C
- Outlet air temperature : 105°C

- Compressed air pressure : 9.5 bar
- Atomising air flow rate : 1000 litres per hour
- Pump speed : 15 rpm (typically this equates to 3 ml per minute).

The yield of the spray drying is between 60 and 70 %.

The spray dried material obtained is micronised in a fluid jet mill (MCC 50, JET Pharma S.A.) under a pressure of 9 bar.

ESCA (electronic spectrometric chemical analysis) data of the micronised particles showed that at least 90 % of the particle surface was covered by the coating layer after micronisation.

The characteristics of the particles before being placed in cartridges are as follows:

mean diameter : 1.5μm (100 % of the particles having a size of less than 5 μm)
water content : 0.6 %
The cartridges are filled manually in a controlled atmosphere room (20 ± 2°C, relative humidity of less than 15%) by successively introducing the micronised material and then the gas. The gas used is pressurised HFA134a gas.

The cartridges are overwrapped with a film which is impermeable to atmospheric moisture.

The finished product thus obtained is stable for several months at room temperature (25°C).

Example 2

0.5g of trehalose and 0.5g of lecithin are dissolved in 100ml of demineralized water at room temperature. After obtaining a colloidal solution, 5g of beclomethasone dipropionate monohydrate (BDP) as micronised particles are dispersed with stirring in the aqueous solution. The suspension thus obtained contains 5% BDP, 0.5% lecithin and 0.5% trehalose.

This suspension is spray dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:

- Inlet air temperature : 160°C
- Outlet air temperature : 105°C
- Compressed air pressure : 9.5 bar
- Atomising air flow rate : 1000 litres per hour
- Pump speed : 15 rpm (typically this equates to 3 ml per minute).

The yield of the spray drying is between 60 and 70%.

The spray dried material obtained is micronised in a fluid jet mill (MCC 50, JET Pharma S.A.) under a pressure of 9 bar.

The particles, before being placed in cartridges, have a mean diameter of 1.5 µm (100% of the particles having a size of less than 5 µm).

The cartridges are filled manually in a controlled atmosphere room (20 ± 2°C, relative humidity of less than 15 %) by successively introducing the micronised material and then the gas. The gas used is pressurised HFA134a gas.

The cartridges are overwrapped with a film which is impermeable to atmospheric moisture.

Example 3

20g of micronised particles of beclomethasone dipropionate monohydrate are triturated with 1g of lecithin in a mortar until a homogeneous physical mixture is obtained. 2g of lactose are dissolved in 100ml of demineralized water at room temperature. The BDP/lecithin physical mixture is subsequently dispersed with stirring in the aqueous lactose solution. The suspension thus obtained contains 20% BDP, 1% lecithin and 2% lactose.

This suspension is spray dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:

- Inlet air temperature : 145°C
- Outlet air temperature : 110°C
- Compressed air pressure : 6 bar
- Atomising air flow rate : 400 litres per hour
- Pump speed : 15 rpm (typically this equates to 3 ml per minute).

The yield of the spray drying is approximately 10%.

The spray dried material obtained is micronised in a fluid jet mill (MCC 50, JET Pharma S.A.) under a pressure of 9 bar.

The characteristics of the particles, before being placed in cartridges, are as follows:

mean diameter: 1.5µm (100% of the particles having a size of less than 5µm)
water content: 0.9%

The cartridges are filled manually in a controlled atmosphere room (20 ± 2°C, relative humidity of less than 15%) by successively introducing the micronised material and then the gas. The gas used is pressurised HFA134a gas.

The cartridges are overwrapped with a film which is impermeable to atmospheric moisture.

Example 4

2g of lactose and 2g of lecithin are dissolved in 100ml of demineralized water at room temperature. After obtaining a colloidal solution, 20g of beclomethasone dipropionate monohydrate (BDP) as micronised particles are dispersed with stirring in the aqueous solution. The suspension thus obtained contains 20% BDP, 2% lecithin and 2% lactose.

This suspension is then spray dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:

- Inlet air temperature : 150°C
- Outlet air temperature : 100°C
- Compressed air pressure : 6 bar
- Atomising air flow rate : 400 litres per hour
- Pump speed : 15 rpm (typically this equates to 3 ml per minute).

The yield of the spray drying is between 50 and 60%.

The spray dried material is micronised in a fluid jet mill (MCC 50, JET Pharma S.A.) under a pressure of 9 bar.

ESCA data of the micronised particles showed that at least 90 % of the particle surface was still covered by the coating layer after micronisation.

The particles, before being placed in cartridges, have a mean diameter of 1.5 μm (100% of the particles having a size of less than 5 μm).
The cartridges are filled manually in a controlled atmosphere room (20 ± 2°C, relative humidity of less than 15%) by successively introducing the micronised material and then the gas. The gas used is pressurised HFA134a gas.

The cartridges are overwrapped with a film which is impermeable to atmospheric moisture.

Example 5

2g of lecithin are dissolved in 100ml of demineralized water at room temperature. 20g of beclomethasone dipropionate monohydrate are pre-mixed with 2g of lactose and the blend dispersed under stirring in the lecithin aqueous solution.

The suspension is spray dried in a Büchi 191 Mini Spray Dryer with parameters as described in Example 4.

The particles, before being placed in cartridges, have a mean diameter of 1.5 μm (100% of the particles having a size of less than 5μm).
The cartridges are filled manually in a controlled atmosphere room (20 ± 2°C, relative humidity of less than 15%) by successively introducing the micronised material and then pressurised HFA134a gas.

The cartridges are overwrapped with a film which is impermeable to atmospheric moisture.

Cartridges were prepared with composition on analysis as follows:

For a 250µg/dose product (63µl metering valve):

BDP:	40mg
Lecithin:	4mg
Lactose	4mg
HFA134a	11.952g

For a 100µg/dose product (63µl metering valve):

BDP:	16mg
Lecithin:	1.6mg
Lactose	1.6mg
HFA134a	11.981g

For a 50µg/dose product (63µl metering valve):

BDP:	8mg
Lecithin:	0.8mg
Lactose	0.8mg
HFA134a	11.990g

Example 6

15g of lecithin are dissolved in 1000ml of demineralized water at room temperature (20°C ± 2°C). 150g of beclomethasone dipropionate monohydrate are pre-mixed with 15g of lactose and the blend dispersed under stirring in the lecithin aqueous solution.

The suspension is spray dried in a NIRO Minor Mobile spray dryer using the following parameters:

- Inlet air temperature: 160°C
- Outlet air temperature: 93°C
- Compressed air pressure (rotary atomiser): 6 bars (32 000 rpm)
- Atomising air flow rate: $100m^3/h$
- Pump speed: 353ml per hour

The yield of the spray drying is between 50 and 90%. The water content of the powder is between 0.5 and 1% (m/m).

The particles prior to micronisation have a mean diameter of 23.6μm .

The spray dried material is micronised in a fluid jet mill (MCC 50, JET Pharma S.A.).

The particles before being placed in cartridges, have a mean diameter of 1.5μm (100% of the particles having a size of less than 5μm).

The cartridges are filled automatically in a controlled atmosphere room (20°C+-2°C, relative humidity of less than 15%) by using a filling machine such as a Pamasol system. The micronised material is successively introduced and mixed with HFA 134a and then pressurised HFA134a gas only is used to clean cartridge valves.

The cartridges are overwrapped with a film which is impermeable to atmospheric moisture.

Cartridges are overwrapped and composition analysis gave the following results:

For a 250 µg/dose product (63 µl metering valve):

BDP:	40mg
Lecithin:	4mg
Lactose:	4mg
HFA134a:	11.952g

For a 100µg/dose product (63µl metering valve):

BDP:	16mg
Lecithin:	1.6mg
Lactose:	1.6mg
HFA134a:	11.981g

For a 50µg/dose product (63µl metering valve):

BDP:	8mg
Lecithin:	0.8mg
Lactose:	0.8mg
HFA134a:	11.990g

Example 7

22.5g of lecithin are dissolved in 1500ml of demineralized water at room temperature (20°C ± 2°C). 225g of beclomethasone dipropionate monohydrate are pre-mixed with 22.5g of lactose and the blend is dispersed under stirring in the lecithin aqueous solution.

The suspension is spray dried in a NIRO Minor Mobile spray dryer using the following parameters:

- Inlet air temperature: 160°C
- Outlet air temperature: 87-90°C
- Compressed air pressure (rotary atomiser): 6.5 bars
- Atomising air flow rate: 100m^3/h
- Pump speed: 353ml per hour

The yield of the spray drying is between 50 and 90%. The water content of the powder is between 0.5 and 1% (m/m).

The particles prior to micronisation have a mean diameter of 19μm .

Example 8

22.5g of lecithin are dissolved in 1500ml of demineralized water at room temperature (20°C ± 2°C). 225g of beclomethasone dipropionate monohydrate are pre-mixed with 22.5g of lactose and the blend is dispersed under stirring in the lecithin aqueous solution.

The suspension is spray dried in a NIRO Minor Mobile spray dryer using the following parameters:

- Inlet air temperature: 160°C
- Outlet air temperature: 91-92°C
- Compressed air pressure (rotary atomiser): 6.5 bars
- Atomising air flow rate: 100m^3/h
- Pump speed: 353ml per hour

The yield of the spray drying is between 50 and 90%. The water content of the powder is between 0.5 and 1% (m/m).

The particles prior to micronisation have a mean diameter of 25.3µm .

The spray-dried material is micronised in a fluid jet mill (MCC 50, JET Pharma S.A.).

The particles before being placed in cartridges, have a mean diameter of 1.5µm (100% of the particles having a size of less than 5µm).

Example 9

30g of lecithin are dissolved in 2000ml of demineralized water at room temperature (20°C ± 2°C). 300g of beclomethasone dipropionate monohydrate are pre-mixed with 30g of lactose and the blend dispersed under stirring in the lecithin aqueous solution.

The suspension is spray dried in a NIRO Minor Mobile spray dryer using the following parameters:

- Inlet air temperature: 160°C
- Outlet air temperature: 93-94°C
- Compressed air pressure (rotary atomiser): 6.5 bars
- Atomising air flow rate: 100m³/h
- Pump speed: 480ml per hour

The yield of the spray drying was between 50 and 90%. The water content of the powder is between 0.4 and 1% (m/m).

The particles prior to micronisation have a mean diameter of 21.4μm .

The spray-dried material is micronised in a fluid jet mill (MCC 50, JET Pharma S.A.).

The particles before being placed in cartridges, have a mean diameter of 1.7μm (100% of the particles having a size of less than 5μm).

The cartridges are filled automatically in a controlled atmosphere room (20°C ± 2°C, relative humidity of less than 15%) by using a filling machine such as a Pamasol system. The micronised material is successively introduced and mixed with HFA 134a and then pressurised HFA134a gas only is used to clean cartridges valves.

The cartridges are overwrapped with a film which was impermeable to atmospheric moisture.

Cartridges are overwrapped and composition analysis gave the following results:

For a 250 μg/dose product (63 μl metering valve):

BDP:	40mg
Lecithin:	4mg
Lactose:	4mg
HFA134a:	11.952g

For a 100μg/dose product (63μl metering valve):

BDP:	16mg

Lecithin:	1.6mg
Lactose:	1.6mg
HFA134a:	11.981g

For a 50µg/dose product (63µl metering valve):

BDP:	8mg
Lecithin:	0.8mg
Lactose:	0.8mg
HFA134a:	11.990g

Example 10

30g of lecithin are dissolved in 2000ml of demineralized water at room temperature (20°C ± 2°C). 300g of beclomethasone dipropionate monohydrate are pre-mixed with 30g of lactose and the blend dispersed under stirring in the lecithin aqueous solution.

The suspension is spray dried in a NIRO Minor Mobile spray dryer using the following parameters:

- Inlet air temperature: 160°C
- Outlet air temperature: 88-94°C
- Compressed air pressure (rotary atomiser): 6.5 bars
- Atomising air flow rate: 100m^3/h
- Pump speed: 480ml per hour

The yield of the spray drying is between 80 and 90%. The particles prior to micronisation have a mean diameter of 12.5 µm .

The spray-dried material is micronised in a fluid jet mill (MCC 50, JET Pharma S.A.).

The particles before being placed in cartridges, have a mean diameter of 1.5µm (100% of the particles having a size of less than 5µm).

Example 11

15g of lecithin are dissolved in 1000ml of demineralized water at room temperature (20°C ± 2°C). 150g of beclomethasone dipropionate monohydrate are pre-mixed with 15g of lactose and the blend dispersed under stirring in the lecithin aqueous solution.

The suspension is spray dried in a NIRO Minor Mobile spray dryer using the following parameters:

- Inlet air temperature: 200°C
- Outlet air temperature: 88-94°C
- Compressed air pressure (two fluid nozzle atomiser): 4 bars
- Atomising air flow rate: 100m^3/h
- Pump speed: 480ml per hour

The yield of the spray drying is between 50 and 90%.

The spray-dried material is micronised in a fluid jet mill (MCC 50, JET Pharma S.A.).

The particles before being placed in cartridges, have a mean diameter of 1.5µm (100% of the particles having a size of less than 5µm).

The cartridges are filled manually in a controlled atmosphere room (20°C ± 2°C, relative humidity of less than 15%) by successively introducing the micronised material and then pressurised HFA134a gas.

The cartridges are overwrapped with a film which was impermeable to atmospheric moisture.

Cartridges are overwrapped and composition analysis gave the following results:

For a 250 µg/dose product (63 µl metering valve):

BDP:	40mg
Lecithin:	4mg
Lactose:	4mg
HFA134a:	11.952g

Example 12

30g of lecithin are dissolved in 2000ml of demineralized water at room temperature (20°C ± 2°C). 150g of beclomethasone dipropionate monohydrate are pre-mixed with 30g of lactose and the blend dispersed under stirring in the lecithin aqueous solution.

The suspension is spray dried in a NIRO Minor Mobile spray dryer using the following parameters:

- Inlet air temperature: 150°C
- Outlet air temperature: 83-90°C
- Compressed air pressure (two fluid nozzle atomiser): 6 bars
- Atomising air flow rate: 100m^3/h

- Pump speed: 1.41kg/h

The yield of the spray drying is between 50 and 90%.

The spray-dried material is micronised in a fluid jet mill (MCC 50, JET Pharma S.A.).

The particles before being placed in cartridges, have a mean diameter of 1.5µm (100% of the particles having a size of less than 5µm).

The cartridges are filled manually in a controlled atmosphere room (20°C ± 2°C, relative humidity of less than 15%) by successively introducing the micronised material and then pressurised HFA134a gas.

The cartridges are overwrapped with a film which is impermeable to atmospheric moisture.

Cartridges are overwrapped and composition analysis gave the following results:

For a 250 µg/dose product (63 µl metering valve):

BDP:	40mg
Lecithin:	4mg
Lactose:	4mg
HFA134a:	11.952g

Example 13

30g of lecithin are dissolved in 2000ml of demineralized water at room temperature (20°C ± 2°C). 300g of beclomethasone dipropionate monohydrate

are pre-mixed with 30g of lactose and the blend dispersed under stirring in the lecithin aqueous solution.

The suspension is spray dried in a NIRO Minor Mobile spray dryer using the following parameters:

- Inlet air temperature: 170°C
- Outlet air temperature: 83-90°C
- Compressed air pressure (two fluid nozzle atomiser): 6 bars
- Atomising air flow rate: $100m^3/h$
- Pump speed: 2.33kg/h

The yield of the spray drying is between 50 and 90%.

The spray-dried material is micronised in a fluid jet mill (MCC 50, JET Pharma S.A.).

The particles before being placed in cartridges, have a mean diameter of 1.5µm (100% of the particles having a size of less than 5µm).

The cartridges are filled manually in a controlled atmosphere room (20°C ± 2°C, relative humidity of less than 15%) by successively introducing the micronised material and then pressurised HFA134a gas.

The cartridges are overwrapped with a film which is impermeable to atmospheric moisture.
Cartridges are overwrapped and composition analysis gave the following results:

For a 250 µg/dose product (63 µl metering valve):

BDP:	40mg
Lecithin:	4mg
Lactose:	4mg
HFA134a:	11.952g

Example 14

2g of lecithin may be dissolved in 200ml of demineralized water at room temperature (20°C ± 2°C). 10g of salmeterol xinafoate as micronized particles are pre-mixed with 2g of lactose and the blend dispersed under stirring in the lecithin aqueous solution. The suspension thus obtained contains 5% salmeterol xinafoate, 1% lecithin and 1% lactose.

The suspension may then be spray dried in a Büchi 191 Mini Spray Dryer with the following parameters:

- Inlet air Temperature: 105°C
- Outlet air Temperature: 58°C
- Compressed air pressure: 7 bars
- Atomising air flow rate: 800 Nl/h
- Drying air flow : 28 m^3/h
- Feed flow: 5 ml/h

The yield of the spray drying should be around 70%. The water content of powder should be less than 0.5% (m/m).

The particles before being micronized should have a mean diameter between 2 and 5µm.

The spray dried material obtained may be micronized in a fluid jet mill (MC 50, JET Pharma S.A.) under a pressure of 8 bars.

The particles before being placed in cartridges should have a mean diameter around 1.5μm

The cartridges may be filled manually by successively introducing the micronized material and then pressurised HFA 134a gas.

CLAIMS

1. A pharmaceutical aerosol formulation, characterised in that it comprises:

(A) a therapeutic agent in the form of particles coated by at least one coating excipient and at least one surfactant, in suspension in
(B) a liquefied propellant gas.

2. A pharmaceutical aerosol formulation according to Claim 1, characterised in that the drug is a therapeutic agent which can be administered by the pulmonary route and which is insoluble in the suspending medium used for the preparation of the formulation.

3. A pharmaceutical aerosol formulation according to Claim 2, characterised in that the therapeutic agent is chosen from beclomethasone dipropionate, salbutamol (eg as sulphate or free base), salmeterol (eg as 1-hydroxy-2-naphoate salt), fluticasone propionate or solvates thereof.

4. A pharmaceutical aerosol formulation according to Claim 3, characterised in that the therapeutic agent is beclomethasone dipropionate or a solvate thereof, in particular beclomethasone dipropionate monohydrate.

5. A pharmaceutical aerosol formulation according to Claim 3, characterised in that it may contain a combination of two or more therapeutic agents.

6. A pharmaceutical aerosol formulation according to any one of Claims 1 to 4, characterised in that the excipient for coating the particles is an excipient which can be administered by the pulmonary route, which is soluble in the

suspending medium used to prepare the formulation, chosen from mono-, di- or polysaccharides.

7. A pharmaceutical aerosol formulation according to Claim 6, characterised in that the coating excipient is chosen from mannitol, lactose, trehalose, dextrose, microcrystalline cellulose, sodium carboxymethylcellulose, methylhydroxypropylcellulose or sorbitol.

8. A pharmaceutical aerosol formulation according to Claim 7, characterised in that the coating excipient is lactose or trehalose.

9. A pharmaceutical aerosol formulation according to any one of Claims 1 to 8, characterised in that the surfactant is a surfactant which can be administered by the pulmonary route chosen from non-ionic, anionic and cationic surfactants.

10. A pharmaceutical aerosol formulation according to Claim 9, characterised in that said surfactant is chosen from oleic acid, sorbitan trioleate, sorbitan monooleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monooleate, natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of ethylene oxide and of propylene oxide, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol 400, glyceryl monolaurate, cetylpyridinium chloride or benzalkonium chloride.

11. A pharmaceutical aerosol formulation according to Claim 10, characterised in that the surfactant is lecithin.

12. A pharmaceutical aerosol formulation according to any one of Claims 1 to 11, characterised in that the drug particles are additionally coated by a vegetable oil.

13. A pharmaceutical aerosol formulation according to Claim 12, characterised in that the vegetable oil is chosen from olive oil, corn oil, cottonseed oil and sunflower seed oil.

14. A pharmaceutical aerosol formulation according to any one of Claims 1 to 13, characterised in that the propellant is a liquefied gas which is a non-solvent for the coated drug particles chosen from C_{1-4} hydrochlorofluorocarbons, C_{1-4} hydrofluorocarbons and C_{1-4} perfluorocarbons or mixtures thereof.

15. A pharmaceutical aerosol formulation according to Claim 14, characterised in that the propellant is 1,1,1,2-tetrafluoroethane.

16. A pharmaceutical aerosol formulation according to any one of Claims 1 to 15, characterised in that the mean size of the coated drug particles is within the range from 0.5 to 10 μm.

17. A pharmaceutical aerosol formulation according to Claim 16, characterised in that the mean size of the coated drug particles is within the range from 1 to 5 μm.

18. A pharmaceutical aerosol formulation according to any one of Claims 1 to 17, characterised in that it contains, besides components (A) and (B), additional ingredients such as solvents or surfactants other than those coated on the drug particles.

19. A pharmaceutical aerosol formulation according to any one of Claims 1 to 17, characterised in that it does not contain ingredients other than the drug particles (A) and the propellant (B).

20. A process for the preparation of a pharmaceutical aerosol formulation according to any one of Claims 1 to 19, characterised in that it comprises the stages which consist

(a) in preparing a suspension containing

- the therapeutic agent in the form of particles,
- a suspending medium which is a non-solvent for the therapeutic agent,
- the coating excipient dissolved in the suspending medium and
- the surfactant;

(b) in spray drying the suspension of the active principle obtained in stage (a), so as to obtain drug particles coated by the excipient and by the surfactant;

(c) suspending the coated drug particles obtained in stage (b) in the liquefied propellant gas.

21. A process for the preparation of a pharmaceutical aerosol formulation according to Claim 20, characterised in that it comprises an additional stage of size reduction of the coated particles obtained by spray drying before suspension in the propellant.

22. A process for the preparation of a pharmaceutical aerosol formulation according to Claim 20 or 21, characterised in that the mean size of the coated drug particles is within the range from 0.5 to 10 µm.

23. A process for the preparation of a pharmaceutical aerosol formulation according to Claim 22, characterised in that the mean size of the coated drug particles is between 1 µm and 5 µm.

24. A process for the preparation of a pharmaceutical aerosol formulation according to any one of Claims 20 to 23, characterised in that the suspending medium is a medium which is a non-solvent for the drug and a solvent for the coating excipient.

25. A process for the preparation of a pharmaceutical aerosol formulation according to Claim 24, characterised in that the suspending medium is water.

26. A process for the preparation of a pharmaceutical aerosol formulation according to any one of Claims 20 to 25, characterised in that the stage of preparation of the suspension (stage (a)) consists in directly suspending the drug particles in the suspending medium containing the dissolved coating excipient and the surfactant.

27. A process for the preparation of a pharmaceutical aerosol formulation according to any one of Claims 20 to 25, characterised in that the stage of preparation of the suspension (stage (a)) comprises two successive stages which consist

(i) in re-absorbing the surfactant onto the drug particles, and then

(ii) in suspending the drug particles carrying the surfactant in the suspending medium containing, in the dissolved form, the coating excipient.

28. A process for the preparation of a pharmaceutical aerosol formulation according to any one of Claims 20 to 27, characterised in that the content of therapeutic agent in the suspension obtained in stage (a) is within the range from 1 to 40 % (mass/volume).

29. A process for the preparation of a pharmaceutical aerosol formulation according to Claim 28, characterised in that the content of therapeutic agent in the suspension is within the range from 5 to 20% (mass/volume).

30. A process for the preparation of a pharmaceutical aerosol formulation according to any one of Claims 20 to 29, characterised in that the surfactant/drug ratio in the suspension of stage (a) is within the range from 1 to 20 % by weight.

31. A process for the preparation of a pharmaceutical aerosol formulation according to Claim 30, characterised in that the surfactant/drug ratio is within the range from 5 to 10 % by weight.

32. A process for the preparation of a pharmaceutical aerosol formulation according to any one of Claims 20 to 31, characterised in that the coating excipient/drug ratio in the suspension of stage (a) is within the range from 1 to 20 % by weight.

33. A process for the preparation of a pharmaceutical aerosol formulation according to Claim 32, characterised in that the coating excipient/drug ratio is within the range from 5 to 10 % by weight.

34. A process for the preparation of a pharmaceutical aerosol formulation according to any one of Claims 20 to 33, characterised in that it comprises successively filling cartridges with the particles obtained after spray drying or micronisation and then with the propellant.

35. A process for the preparation of a pharmaceutical aerosol formulation according to any one of Claims 20 to 34, characterised in that it comprises filling cartridges in a single stage by introduction of a suspension of the coated particles, which are obtained after spray drying or micronisation, in the propellant.

36. A process for the preparation of a pharmaceutical aerosol formulation according to any one of Claims 20 to 34, characterised in that it comprises filling cartridges firstly by introduction of the coated particles, which are obtained after spray drying or micronisation, and secondly by introduction of the propellant.

37. A process for the preparation of a pharmaceutical aerosol formulation according to any one of Claims 34 to 36, characterised in that it comprises overwrapping filled cartridges with a film which is impermeable to atmospheric moisture.

38. Particles of pharmaceutical active principles suitable for use, in combination with a propellant gas, in a pharmaceutical aerosol formulation according to any one of Claims 1 to 19, characterised in that they are composed of a thera-

peutic agent coated by at least one coating excipient and at least one surfactant.

39. Particles of pharmaceutical active principles obtainable by a process which comprises the stages which consist

(a) in preparing a suspension containing

- the therapeutic agent in the form of particles,
- a suspending medium which is a non-solvent for the therapeutic agent,
- the coating excipient dissolved in the suspending medium and
- the surfactant; and

(b) in spray drying the suspension of the active principle obtained in stage (a), so as to obtain drug particles coated by the excipient and by the surfactant.

40. Particles according to claim 39 wherein the therapeutic agent is beclomethasone dipropionate or a solvate thereof, the suspending medium is water, the coating excipient is lactose and the surfactant is lecithin.

41. A pharmaceutical aerosol formulation obtainable by a process according to any one of claims 20 to 33.

42. A cartridge containing a pharmaceutical aerosol formulation according to any one of claims 1 to 19 and 41.

43. A cartridge according to claim 42 overwrapped with a film which is impermeable to atmospheric moisture.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/02535

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/12 A61K9/16 A61K31/57

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 655 237 A (HOECHST AG) 31 May 1995 (1995-05-31)	1,6-11, 14,15, 18,38
A	page 3, column 3, line 48 - column 4, line 26 page 4, column 5, line 29-34 page 4, column 5, line 43-54 example 9 claims ---	2,3,20, 24,26, 30,32, 34,36, 39,41,42

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
26 July 1999	02/08/1999

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/02535

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X A	US 5 141 674 A (LEIGH STEVEN) 25 August 1992 (1992-08-25) column 3, line 32-35 column 3, line 54 - column 4, line 25 examples 9,10 claims 1,2,4,5,9-11,23,28 ---	1-4, 6-11,16, 17,19,38 20, 22-24,27
X	EP 0 257 915 A (INNOVATA BIOMED LTD) 2 March 1988 (1988-03-02) page 2, line 38-43 page 3, line 15-24 page 3, line 39 - page 4, line 4 examples 3,5 claims ---	1-3,9, 10,20, 34,36, 38,39
A	WO 96 19968 A (GLAXO GROUP LTD ;GREEN ALEXANDER PETER (GB)) 4 July 1996 (1996-07-04) page 1, line 34 - page 2, line 16 page 3, line 11-32 page 5, line 11-14 page 5, line 31 - page 6, line 8 page 6, line 23-28 page 7, line 10-14 ---	1-43
A	WO 97 36574 A (GLAXO GROUP LTD ;OORT MICHIEL VAN (US); SACCHETTI MARK J (US)) 9 October 1997 (1997-10-09) page 9, line 20-25 page 11, line 4-9 example 3 page 10, line 7-21 page 14, line 1-16 claims ---	1-43
P,X	WO 98 29098 A (INHALE THERAPEUTIC SYSTEMS INC) 9 July 1998 (1998-07-09) page 3, line 10-33 page 6, line 27-37 page 9, line 28-35 page 14, line 37 - page 15, line 17 page 23 - page 24; table 2 claims -----	38,39, 41,42

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

rnational Application No
PCT/EP 99/02535

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 0655237	A	31-05-1995	AU	676390	B	06-03-1997
			AU	7905194	A	08-06-1995
			CA	2136704	A	28-05-1995
			FI	945524	A	28-05-1995
			HU	75152	A	28-04-1997
			JP	7187996	A	25-07-1995
			NO	944526	A	29-05-1995
			NZ	264993	A	26-03-1996
			ZA	9409378	A	11-08-1995
US 5141674	A	25-08-1992	AT	75606	T	15-05-1992
			DE	3585967	A	11-06-1992
			EP	0158441	A	16-10-1985
			JP	7053661	B	07-06-1995
			JP	61044808	A	04-03-1986
			US	5004611	A	02-04-1991
			US	5053217	A	01-10-1991
			AT	83145	T	15-12-1992
			DE	3783039	A	21-01-1993
			EP	0309464	A	05-04-1989
			WO	8707502	A	17-12-1987
			JP	1502979	T	12-10-1989
			JP	2779165	B	23-07-1998
EP 0257915	A	02-03-1988	AT	86482	T	15-03-1993
			AU	612591	B	18-07-1991
			AU	7754987	A	08-03-1988
			CA	1302258	A	02-06-1992
			DE	3784594	A	15-04-1993
			DE	3784594	T	05-01-1994
			DK	195988	A	08-06-1988
			EP	0318492	A	07-06-1989
			ES	2053549	T	01-08-1994
			WO	8801165	A	25-02-1988
			GB	2211413	A,B	05-07-1989
			IE	59720	B	23-03-1994
			JP	1503534	T	30-11-1989
			JP	2765700	B	18-06-1998
			KR	9514440	B	28-11-1995
			NO	176784	B	20-02-1995
			PT	85521	A,B	01-09-1987
			US	5384133	A	24-01-1995
			ZA	8705937	A	18-02-1988
WO 9619968	A	04-07-1996	AU	4346996	A	19-07-1996
			EP	0799024	A	08-10-1997
			JP	10511376	T	04-11-1998
WO 9736574	A	09-10-1997	AU	2292197	A	22-10-1997
			CA	2250217	A	09-10-1997
			EP	0904056	A	31-03-1999
WO 9829098	A	09-07-1998	AU	5719798	A	31-07-1998
			AU	5806898	A	31-07-1998
			AU	5806998	A	31-07-1998
			AU	6014098	A	31-07-1998
			WO	9829096	A	09-07-1998
			WO	9829140	A	09-07-1998

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

rnational Application No
PCT/EP 99/02535

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9829098 A		WO 9829141 A	09-07-1998

Form PCT/ISA/210 (patent family annex) (July 1992)